REVIEW ARTICLE

# The hypocretin/orexin system

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The hypocretins (orexins) are recently described hypothalamic neuropeptides thought to have an important role in the regulation of sleep and arousal states[1]. Their discovery was reported independently by two groups using different techniques. de Lecea *et al*.[2] identified the pro-hormone preprohypocretin, and its peptide products hypocretin-1 (Hcrt-1) and hypocretin-2 (Hcrt-2), by nucleotide sequencing. The discovery of the orexins, orexin-A (Orx-A) and orexin-B (Orx-B), was reported almost simultaneously by Sakurai *et al*.[3] who used the technique of orphan receptor cloning. The terms orexin and hypocretin are synonymous and in this article we will use hypocretin (Hcrt). The finding that cerebrospinal fluid (CSF) levels of these peptides were abnormal in patients with narcolepsy has stimulated research on the potential role of these peptides in human disease. We present here an overview of the pertinent findings from animal studies and a review of the published data from human studies, with a particular emphasis on narcolepsy. Finally, we consider the possible roles of these peptides in neurological and psychiatric disorders.

## BACKGROUND

### Identification of the peptides

In 1996, a set of neuropeptides related to the hormone secretin were isolated from the rat lateral hypothalamus by the process of directional tag PCR subtraction cloning[4]. The cloning of the gene for these peptides from rat and mouse, the localization of the peptide-producing cell bodies and a description of some of their efferent projections were first presented in 1997[5,6].

### The receptors

The receptors for these neuropeptides (Hcrtr1 [Orxr1] and Hcrtr2 [Orxr2]) have been identified as G-protein coupled receptors and shown in the rat brain, by analysis of their mRNA, to display a striking distribution[7,8]. The Hcrtr1 receptor has a much higher (100 to 1000-fold) affinity for Hcrt-1 than for Hcrt-2. The Hcrtr2 receptor seems to have equal affinities for both neuropeptides. The distinctive distribution of the receptors has led some authors to hypothesize a sleep-specific role for the Hcrtr1 receptor and a more general role for Hcrtr2 receptor. The receptors have been mapped on human chromosome 1p33 and 6cen, respectively[5,7–9].

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### Projections of the hypocretin system

The hypocretin-producing cell bodies are specific to the hypothalamus and have widespread anatomical projections within the central nervous system of the rat with the densest extra-hypothalamic projection to the noradrenergic locus coeruleus (LC) and lesser projections to the basal ganglia, thalamic regions, the medullary reticular formation, and the nucleus of the solitary tract. There are minor projections to the cortical regions, central and anterior amygdaloid nuclei, and the olfactory bulb[4,10,11]. In humans, the localization of hypocretin-producing cell bodies is restricted to the dorso-lateral hypothalamus with extensive dense projections to the locus coeruleus (LC), dorsal raphe nuclei, amygdala, suprachiasmatic nucleus, basal forebrain, cholinergic brainstem[12,13] and spinal cord (Figure 1)[14].

### Neurochemical actions of the hypocretins

The hypocretins are thought to act primarily as excitatory neurotransmitters[1,2,7]. Systemic and intracerebroventricular administration of hypocretins directly stimulates cells on the LC noradrenergic system in rats and monkeys, suggesting a role for the hypocretins in various central nervous functions related to noradrenergic innervation, including vigilance, attention, learning, and memory[15]. Their actions on serotonin, histamine, acetylcholine and dopamine neurotransmission is also thought to be excitatory and a facilitatory role on gamma-aminobutyric acid (GABA) and glutamate-mediated neurotransmission is suggested[16,17]. In particular, intravenous administration of Hcrt-1 in rats produces a differential release of GABA and glutamate in the hypocretin-dense amygdala compared with the cerebellum, suggesting that modulation of these neurotransmitters is dependent on hypocretin innervation[18].

### Functions of hypocretin

Apart from their primary role in the control of sleep and arousal[1,7], the hypocretins have been implicated in multiple

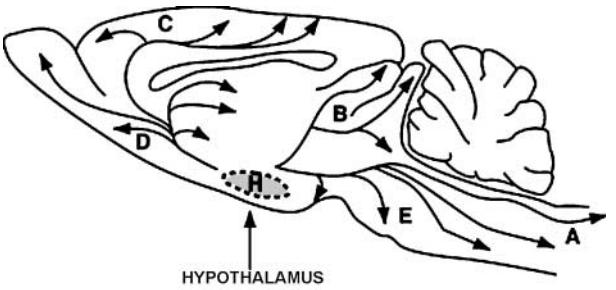


*Figure 1* **Projections of the hypocretin (orexin) system** (A), to cholinergic neurons, reticular formation and spinal cord; (B), to thalamus and basal ganglia; (C), to basal forebrain; (D), to amygdala and dopaminergic neurons including suprachiasmatic nucleus; (E), to locus coeruleus.

functions including feeding and energy regulation[3,16,19–21], neuroendocrine regulation[17,22], gastrointestinal[23] and cardiovascular system[24] control, the regulation of water balance, and the modulation of pain[1]. A role in behaviour is also postulated[25]. The cell bodies responsible for hypocretin synthesis are localized to the tuberal part of the hypothalamus, the so-called feeding centre. The observation that Hcrt-1 increases metabolic rate and the demonstration that insulin-induced hypoglycaemia activates up to one-third of hypocretin containing neurons[21] has led to the suggestion that the hypocretins are mediators of energy metabolism[26]. The neuroendocrine effects of the hypocretins include a lowering of plasma prolactin and growth hormone and an increase in the levels of corticotropin and cortisol, insulin and luteinizing hormone[1,16,17]. Central administration of the hypocretins increases water consumption, stimulates gastric acid secretion and increases gut motility[1,23]. The hypocretins increase mean arterial blood pressure and heart rate[7]. The localization of long descending axonal projections containing hypocretin at all levels of the spinal cord[14] suggests a role in the modulation of sensation and pain. Strong innervation of the caudal region of the sacral cord suggests a role in the regulation of both sympathetic and parasympathetic functions.

## HYPOCRETIN IN NARCOLEPSY

Narcolepsy is a primary disorder of alertness with an estimated prevalence of 0.03–0.05%. It may develop at any age but peak onset is in adolescence with a secondary peak in the fourth decade. The presenting symptom is usually excessive daytime sleepiness, with irresistible sleep attacks during the day. Other symptoms of this syndrome are cataplexy (brief episodes of muscle weakness or paralysis precipitated by strong emotion, such as laughter or surprise), sleep paralysis, which is a symptom due to the persistence of rapid-eye-movement (REM) sleep atonia on waking, and hypnogogic hallucinations or dream-like images, which characteristically occur at sleep onset. Short periods of automatic behaviour may also occur, a reflection of brief intrusions of sleep ('micro-sleeps') into the drowsy state[28].

### Animal studies

In 1999, Lin *et al.*[29] demonstrated a mutation in the hypocretin receptor 2 gene in canine narcolepsy. The subsequent finding that mice lacking hypocretin receptors show behavioural arrests similar to symptoms of narcolepsy-cataplexy—i.e. direct transitions from wakefulness to REM sleep, gait disturbance preceding and rocking activity during behavioural arrest episodes[30,31]—led to a recognition of the potential importance of the hypocretins in sleep, arousal and activation. The animal models of narcolepsy show some variability in the defect causing the narcolepsy-like syndrome. In the mouse model, disruption of both types of hypocretin receptor pathways, Hcrtr1 and Hcrtr2, is necessary to produce the narcoleptic findings[30–33] whereas in the canine model of narcolepsy the predominant defect is at the Hcrtr-2 receptor[29]. Intravenous administration of Hcrt-1 to narcoleptic dogs (dobermans) reduces cataplexy and normalizes their sleep and waking durations[34].

### Hypocretin in cerebrospinal fluid

There have been several studies of hypocretin in human CSF. The published work to date has tested for the presence of Hcrt-1 only and not Hcrt-2. CSF hcrt-1 levels in healthy adults are within a narrow range (250–280 pg/mL)[35]. A recent study indicated no significant difference in hypocretin levels with respect to gender or age, and concluded that very low or undetectable CSF hypocretin concentrations are an abnormal finding at any age[36].

The initial study by Nishino *et al.*[35] found that 7 of 9 patients with narcolepsy-cataplexy had undetectable levels of hypocretin in their CSF. Of the 2 patients with detectable hypocretin, one was within the control range and the other had raised levels. Both these patients were indistinguishable from the other patients with narcolepsy. The authors suggested that these patients might have a hypocretin receptor defect rather than a hypocretin production deficiency. Ripley *et al.*[37] have reported undetectable levels of hypocretin in the CSF from 32 of 36 patients tested. In the remaining 4 the hypocretin levels were below the control range.

There have been two studies examining hypocretin cells post mortem in the brains of patients with narcolepsy[12,13]. Both found a striking reduction, to about 10% of the normal number of hypocretin neurons, in narcoleptic brains. In the initial study[12] there was cell loss without gliosis or signs of inflammation. However, in the other study[13] there was evidence of gliosis in the hypocretin cell region, implying that a degenerative process was the cause

of hypocretin cell loss in narcolepsy. Further support for the degenerative hypothesis is their finding of a higher number of astrocytes in the hypothalamus of narcoleptic patients than in controls. The absence of hypocretin neurons can be explained by mechanisms including neurodegeneration, failure of development, reduction in synthesis or release of hypocretins or some mutation in the DNA sequence coding for hypocretin (though only 1 out of the 74 narcoleptic patients screened showed a mutation[12]).

## HYPOCRETIN IN NEUROLOGICAL AND PSYCHIATRIC DISORDERS

The role of hypocretin in other neurological illnesses is yet to be established. A recent study[38] found that CSF hypocretin levels did not differ significantly between two groups, one with neuroimmunological disease and the other with non-neuroimmunological disease, and normal controls. In a subgroup analysis the investigators found that 4 of 10 patients with Guillain–Barré syndrome had significantly lower Hcrt-1 levels than the controls. Another study[37] has demonstrated low CSF hypocretin levels in patients with subarachnoid haemorrhage, acoustic schwannoma and head trauma—perhaps explained by damage to and/or dysfunction of the hypothalamus.

The dense hypocretin projections to the noradrenergic, serotonin, dopaminergic, cholinergic, and GABA/glutamate areas of the brain suggest a possible role in psychiatric and neuropsychiatric disorders[39,40]. The hypocretin system may be important in affective disorders such as major depression and bipolar affective disorder. The monoamine hypothesis (biogenic amine hypothesis) of depression suggests that dysfunctional or deficient neurotransmission of noradrenaline and/or serotonin underlies the symptoms of depression[41–43]. More recently, emphasis has shifted to the possible roles of neuropeptides in the aetiology and treatment of depression[44–49]. Involvement of the hypocretin system in depression is suggested on neuroanatomical and pharmacological grounds. The only substance known to innervate all the relevant areas of the brain implicated in the neurobiology of depression is hypocretin and the excitatory innervation of the LC and dorsal raphe region, the stimulation of dopamine and acetylcholine and the prohistaminergic actions all point to an antidepressant effect. These therapeutic possibilities remain to be clarified by appropriate studies.

## CONCLUSION

There is strong evidence that narcolepsy is associated with abnormalities of the hypocretin neurotransmitter system. Low or undetectable levels of hypocretin are found in most patients but some have normal or raised levels. Thus it has been suggested that there are two variants of narcolepsy. In most patients there seems to be a hypocretin deficiency but there may also be a form with 'hypocretin resistance' due to abnormal hypocretin receptor/post-receptor dynamics leading to overproduction of hypocretin[9,50]. There may be involvement of the hypocretin/orexin system in other disorders of sleep such as primary hypersomnolence, insomnia, and the Kleine-Levin syndrome[10], and a potential role in sleep disorders affecting the ageing population[7,28,41,51,52]. The role of these peptides in other neurological and psychiatric disorders remains putative.

## REFERENCES


1 Sutcliffe JG, de Lecea L. The hypocretins: excitatory neuromodulatory peptides for multiple homeostatic systems, including sleep and feeding. *J Neurosci Res* 2000;**62**:161–8

2 de Lecea L, Kilduff TS, Peyron C, *et al*. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci USA* 1998;**95**:322–7

3 Sakurai T, Amemiya A, Ishii M, *et al*. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G-protein coupled receptors that regulate feeding behaviour. *Cell* 1998;**92**:573–5

4 Gautvik KM, de Lecea L, Gautvik VT, *et al*. Overview of the most prevalent hypothalamus-specific mRNAs, as identified by directional tag PCR subtraction. *Proc Natl Acad Sci USA* 1996;**93**:8733–8

5 Peyron C. Distribution of immunoreactive neurons and fibers for a hypothalamic neuropeptide precursor related to secretin. *Soc Neurosci Abstr* 1997;**23**:2032

6 Sutcliffe JG. Two novel hypothalamic peptides related to secretin derived from a single neuropeptide precursor. *Soc Neurosci Abstr* 1997;**23**:2032

7 Kilduff TS, Peyron C. The hypocretin/orexin ligand-receptor system: implications for sleep and sleep disorders. *TINS* 2000;**23**:359–64

8 Trivedi P, Yu H, MacNeil DJ, Van der Ploeg LH, Guan XM. Distribution of orexin receptor mRNA in the rat brain. *FEBS Lett* 1998;**438**:71–5

9 Chicurel M. The sandman's secrets. *Nature* 2000;**407**:554–6

10 Mignot E. Perspectives in narcolepsy and hypocretin (orexin) research. *Sleep Med* 2000;**1**:87–90

11 Peyron C, Tighe DK, Van den Pol AN, *et al*. Neurones containing hypocretin (orexin) project to multiple neuronal systems. *J Neurosci* 1998;**23**:9996–10015

12 Peyron C, Faraco J, Rogers W, *et al*. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med* 2000;**6**:991–7

13 Thannickal TC, Moore RY, Nienhuis R, *et al*. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 2000;**27**:469–74

14 van den Pol AN. Hypothalamic hypocretin (orexin): robust innervation of the spinal cord. *J Neurosci* 1999;**19**:3171–82

15 Horvath TL, Peyron C, Diane S, *et al*. Hypocretin (orexin) activation and synaptic innervation of the locus coeruleus noradrenergic system. *J Comp Neurol* 1999;**415**:145–59

16 Ida T, Nakahara K, Kuroiwa T, *et al*. Both corticotrophin releasing factor and neuropeptide Y are involved in the effect of orexin (hypocretin) on the food intake in rats. *Neurosci Lett* 2000;**293**:119–22

17 van den Pol AN, Gao XB, Obrietan K, Kilduff TS, Belousov AB. Presynaptic and postsynaptic actions and modulation of neuroendocrine neurones by a new hypothalamic peptide, hypocretin/orexin. *J Neurosci* 1998;**18**:7962–71

18 John J, Wu MF, Kodana T, Siegel JM. Hypocretin-1 (orexin-A) produced changes in glutamate and GABA release: an *in vivo* microdialysis study [Abstract]. *Sleep* 2001;**24**(suppl):A20

**19** Edwards CM, Abusnana S, Sunter D, Murphy KG, Ghaten MA, Bloom SR. The effect of orexins on food intake: comparison with neuropeptide Y, melanin-concentrating hormone and galanin. *J Endocrinol* 1999;**160**:R7–12

**20** Haynes AC, Jackson B, Overend P, *et al*. Effects of single and chronic intracerebroventricular administration of the orexins on feeding in the rat. *Peptides* 1999;**20**:1099–105

**21** Moriguchi T, Sakurai T, Nambu T, Yanagisawa M, Goto K. Neurons containing orexin in the lateral hypothalamic area of the adult rat brain are activated by insulin-induced acute hypoglycemia. *Neurosci Lett* 1999;**264**:101–4

**22** Kuru M, Ueta Y, Serino R, *et al*. Centrally administered orexin–hypocretin activates HPA axis in rats. *Neuroreport* 2000;**11**: 1977–80

**23** Kirchgessner AL, Liu M. Orexin synthesis and response in the gut. *Neuron* 1999;**24**:941–51

**24** Samson WK, Gosnell B, Chang JK, Resch ZT, Murphy TC. Cardiovascular regulatory actions of the hypocretins in brain. *Brain Res* 1999;**831**:248–53

**25** Ida T, Nakahara K, Katayama T, Murakami N, Nakazato M. Effect of lateral cerebroventricular injection of the appetite-stimulating neuropeptides, orexin and neuropeptide Y, on the various behavioural activities of rats. *Brain Res* 1999;**821**:526–9

**26** Chemelli RM, *et al*. Metabolic characterisation of orexin knockout mice [Abstract]. *Sleep* 2001;**24**(suppl):A21

**27** Samson WK, Resch ZT. The hypocretin/orexin story. *Trends Endocrinol Metab* 2000;**11**:257–62

**28** Krahn LE, Black JL, Silber MH. Narcolepsy: new understanding of irresistible sleep. *Mayo Clin Proc* 2001;**76**:185–94

**29** Lin L, Farace J, Li R, *et al*. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell* 1999;**98**:365–76

**30** Chemelli RM, Willie JT, Sinton CM, *et al*. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 1999;**98**:437–51

**31** Kisanuki YY, Chemelli RM, Tokita S, *et al*. Behavioural and polysomnographic characterization of orexin-1 receptor and orexin-2 receptor double knockout mice [Abstract]. *Sleep* 2001;**24**(suppl):A22

**32** Kisanuki YY, Chemelli RM. The role of orexin receptor type-1 (OX1R) in the regulation of sleep [Abstract]. *Sleep* 2000; **23**(suppl):A91

**33** Takita S, Chemelli RM, Willie JT, Yanagisawa M. Behavioural characterisation of orexin-2 receptor (OX2R) knockout mice [Abstract]. *Sleep* 2001;**24**(suppl):A20

**34** John J, Wu MF, Siegel JM. Systemic administration of hypocretin-1 reduces cataplexy and normalizes sleep and waking durations in narcoleptic dogs. *Sleep Res Online* 2000;**3**:23–8

**35** Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 2000; **355**:39–40

**36** Kanbayashi T, Yano T, Ishiguro H, *et al*. Hypocretin (orexin) levels in human lumbar CSF in different age groups [Abstract]. *Sleep* 2001;**24**(suppl):A330

**37** Ripley B, Overeem S, Fujiki N, *et al*. CSF hypocretin levels in various neurological conditions: low levels in narcolepsy and Guillain Barré Syndrome [Abstract]. *Sleep* 2001;**24**(suppl): A322

**38** Kanbayashi T, Ishiguro H, Yano T, *et al*. Hypocretin/orexin concentrations are low in patients with Guillain Barré syndrome [Abstract]. *Sleep* 2001;**24**(suppl):A331–2

**39** Charney DS. Monoamine dysfunction and the pathophysiology and treatment of depression. *J Clin Psychiatry* 1998;**59**:11–14

**40** van den Pol AN. Narcolepsy: a neurodegenerative disease of the hypocretin system? *Neuron* 2000;**27**:415–18

**41** Bunney WE, Davis JM. Noradrenaline in depressive reactions. A review. *Arch Gen Psychiatry* 1965;**13**:483–94

**42** Coppen A. The biochemistry of affective disorders. *Br J Psychiatry* 1967;**113**:1237–64

**43** Miller HL, Delgado PL, Salomon RM, *et al*. Clinical and biochemical effects of catecholamine depletion on antidepressant-induced remission of depression. *Arch Gen Psychiatry* 1996;**53**:117–28

**44** Gold PW, Chrousos G, Kellner C, *et al*. Psychiatric implications of basic and clinical studies with corticotropin-releasing factor. *Am J Psychiatry* 1984;**141**:619–27

**45** Gold PW, Loriaux DL, Roy A, *et al*. Responses to corticotropin-releasing hormone in the hypercorticolism of depression and Cushing's disease. Pathophysiologic and diagnostic implications. *N Engl J Med* 1986;**314**:1329–35

**46** Holsboer F, Van Bardeleben U, Gerken A, Stalla GR, Muller OA. Blunted corticotropin and normal cortisol response to human corticotropin-releasing factor in depression. *N Engl J Med* 1984;**311**:1127

**47** Kramer MS, Cutler N, Feighner J, *et al*. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science* 1998;**281**:1640–5

**48** Wong M-L, Licinio J. Research and treatment approaches to depression. *Nat Rev Neurosci* 2001;**2**:343–51

**49** Zobel AW, Nickel T, Kunzel ME, *et al*. Effects of high-affinity corticotropin releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res* 2000;**34**:171–81

**50** Melberg A, Ripley B, Lin L, Hetta J, Mignot E, Nishino S. Hypocretin deficiency in familial symptomatic narcolepsy. *Ann Neurol* 2001;**49**:136–7

**51** Salin-Pascual RJ. The role of the hypothalamic neuropeptides hypocretin/orexin the sleep-wake cycle. *Isr Med Assoc J* 2001;**3**: 144–6

**52** Scammell TE, Estabrooke IV, McCarthy MT, *et al*. Hypothalamic arousal regions are activated during Modafinil-induced wakefulness. *J Neurosci* 2000;**20**:8620–8